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UNIVERSITY OF WESTERN ONTARIO
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SYMPOSIUM ON UROLOGY

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REPORT ON DIABINESE

A New Advance in the

Oral Treatment of Diabetes

Table X is a correlation of the response to Diabinese with failure of response to tolbutamide. Patients who were diagnosed as showing primary or secondary ... failure of tolbutamide treatment of their diabetes were given Diabinese. Patients with these diagnoses were studied particularly thoroughly by Dr. Garfield Duncan and his group (Code 29), and by Dr. Samuel Sugar (Code 97), with Diabinese, 62% of those patients having a primary therapeutic failure of response to tolbutamide showed an excellent or fair response to Diabinese. Of those patients diagnosed as secondary tolbutamide therapeutic failures, 86% showed an excellent or fair response when treated with Diabinese.[1]

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1. Summary of Diabinese Study Program

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CONTRIBUTIONS will be accepted with the understanding that they are made solely to this publication. Articles should be of practical value to students and medical practitioners. Original research work is most welcome. Articles should not be longer than 3,000 words, and we will more readily accept those of shorter length. Introduction and summary of conclusions should be included. Drawings and photographs will be accepted, the former to be in black ink and drawn clearly.

All articles submitted *must be typewritten*, on one side of paper only, with double spacing and one and one-half inch margins on each side. Canadian Press (American) spelling must be adhered to. The format for references is as follows: *For books*: Author(s): title of book, publisher, place, year. *For journals*: (Author(s): name of journal (abbreviated as in the World List of Scientific Periodicals), volume: page, year.

Foreword - Symposium on Urology

Life consists of the past, present, and future; living consists only of the present. A students' Journal effervesces with the future. However, it is necessary to take a look at the past to determine on what foundation the future is built.

Urology in western Ontario is on an unshakeable foundation, a foundation made of the finest and most durable material, yet possessing an unsurpassed kindness, sincere concern for one's patients, and ability to care for them. I refer to the late Dr. Eldon D. Busby—not only my teacher, but still a constant companion and guide to me. To have known Dr. Busby is surely enough to convince anyone that this life possesses a "hereafter". His influence will outlive us all.

Born in Owen Sound in 1893, he graduated, a gold medallist, from McGill University in 1913. His medical education was obtained at Harvard University, and his surgical and urological training was under Dr. Hugh Cabot—one of America's pioneers in Urology.

Dr. Busby came to London in 1923 and was the first Professor of Urology in the U. of W. O. Medical School. Amongst other things, he introduced transurethral surgery to western Ontario, and later published, through the Royal College of Surgeons of Canada, one of the largest personal series of transurethral prostatectomies ever published. Although the first and foremost Urologist of this area, Dr. Busby is also remembered for his diagnostic and operative ability as a general surgeon. As an obligation to such a man, those of us who are called upon to humbly attempt to fill the void have given and will continue to give ourselves to the advancement of Urology.

Urology reaches into every aspect of medicine, including pediatrics, neurology, endocrinology, vascular surgery, chest surgery, internal medicine, etc. The training of a "complete" urologist is therefore a long and arduous task, and should only be undertaken by those with a zest for living and a large capacity for work. As in any profession, happiness and satisfaction demand a balance between ambition and ability. If real progress is to be made, not only must this ratio be correct, but one must possess a large amount of both.

In the past few years, many new procedures, both diagnostic and surgical, have been introduced into urology, always with a view to improving the lot of the patient. Such diagnostic measures as needle biopsy of the prostate and kidney, arteriography and pneumography, along with such surgical procedures as endoscopic ureterolithotomy, thoracoabdominal nephrectomy, pyelolithotripsy, and the use of an isolated loop of ileum to replace ureters and/or bladder, are some of these advancements. During the past year the first experimental urological surgery was carried out on a group of dogs at the Medical School. There are further such problems to be tackled in the future.

Whether you choose a specialty or general practice, I trust your necessity for a consulting urologist will only be surpassed by his willingness and ability to serve.

I appreciate this opportunity to place before the readers of this journal my thoughts on urology.

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Assistant Professor of Surgery,
The University of Western Ontario

The Neurogenic Bladder

JAMES A. BAIN, '59

DEFINITION

The neurogenic bladder is a condition in which the bladder functions abnormally as a result of a lesion in the central nervous system which causes imbalance between the forces of expulsion and the forces of retention.

NERVE SUPPLY OF THE BLADDER

The bladder is supplied by 3 groups of nerves:

1. Somatic nerve supply, via the internal pudendal nerve from S.2.3.4, gives motor innervation to the external sphincter and sensory appreciation to the posterior urethra.

2. Parasympathetic nerve supply, via the pelvic nerves (nervi erigentes) from S.2.3.4, gives motor innervation to the detrusor muscle and carries sensory afferents from the bladder. These are the main nerves of micturition.

3. Sympathetic nerve supply, via the hypogastric nerves which arise from branches of the lumbar sympathetic ganglia and aortic plexus, is motor to the seminal vesicles, prostate gland, and ejaculatory duct as well as trophic to the bladder. Section of the sympathetic does not affect micturition.

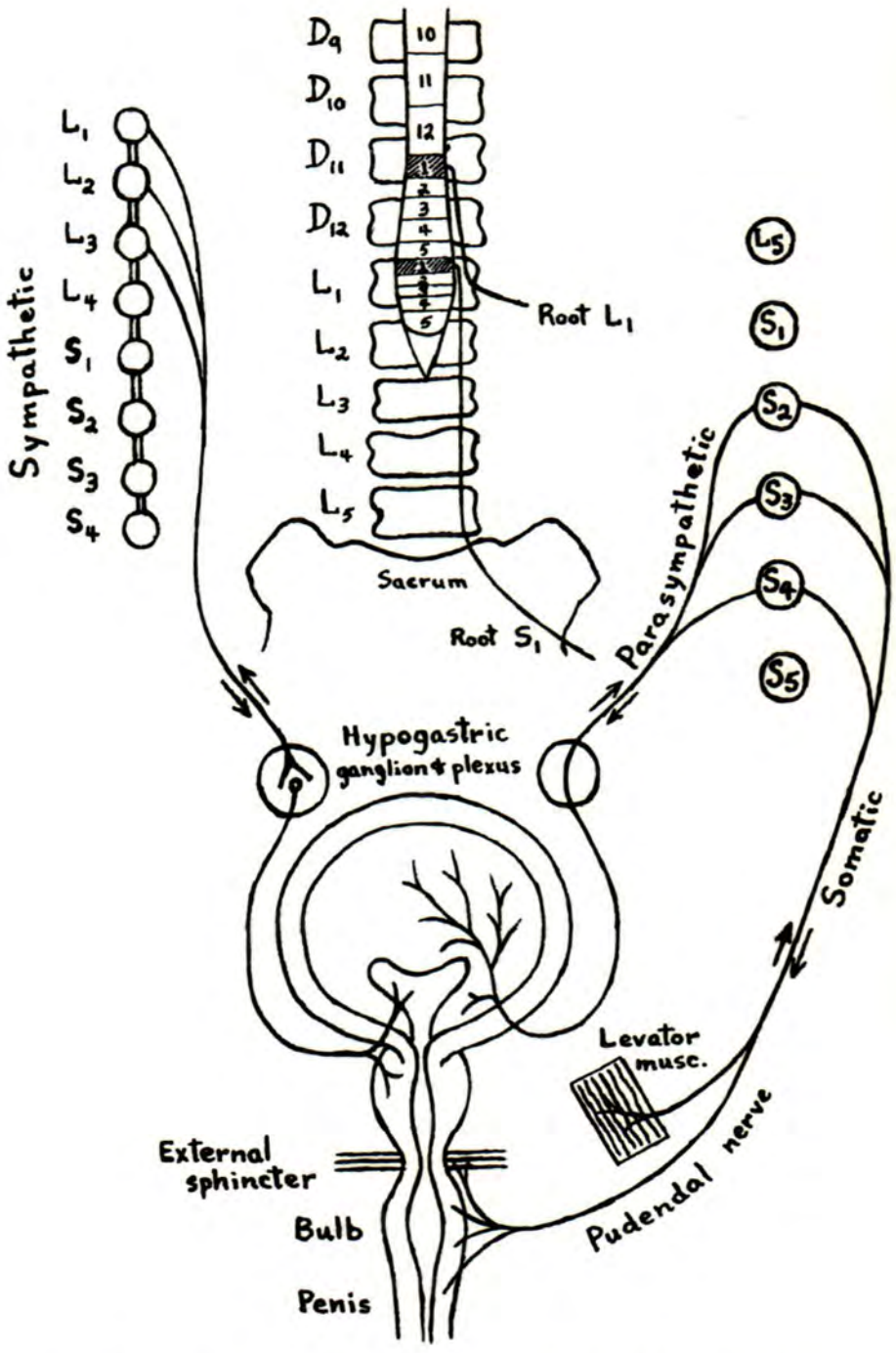
There is a micturition center in the sacral segments of the spinal cord which has never been localized. The sensory afferent and motor efferent components are contained in the parasympatheic pelvic nerves and connected in the cord by a connecting neurone. The micturition center is inhibited by higher centers probably in the brain stem and hypothalmus for subconscious control and in the cerebral cortex for appreciative and active control.

An important sensory function of the bladder wall which arises from the muscular layer is the appreciation of filling. This "stretch reflex" is a basic function of the bladder muscle which responds as a spinal reflex by steadily relaxing so that an increasing volume of urine may be held at low pressure until the bladder becomes full. When the pressure rises steeply the "urge to void" is appreciated. This sensation is carried via the pelvic parasympathetic nerves.

BLADDER CONTROL AND THE PHYSIOLOGY OF MICTURITION

As the bladder fills, the bladder wall relaxes to hold its content at a low pressure, normal intravesical pressure being about 7-8 cm. of water. The low intravesical pressure is considered to be the result of the natural tone of the smooth muscle of the detrusor, an inherent property of smooth muscle which is not dependent on the nerve supply. The contraction of the detrusor muscle is probably due to a stretch reflex through afferent, connecting, and efferent neurones with a reflex micturition center in the conus medullaris. The "urge to void" comes only when the pressure rises to 14-16 cm. of water. The spinal center initiates rhythmic contractions of the detrusor so normally the muscle would contract without the control from the higher centers. When the "urge to void" becomes urgent, if convenient, voluntary micturition ensues, and if inconvenient, active voluntary retraint is required. The external sphincter and accessory muscles of the pelvic floor are used to inhibit micturition.

Voluntary micturition can be initiated at any stage of filling. When the bladder is



The Nerve Supply of the Bladder and Relation of Lumbar and Sacral Segments of the Spinal Cord to the Vertebrae

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almost empty, initiation of the act often requires help from straining to increase the ntravesical pressure. Normally, however, the detrusor contracts when the cerebral inhibition is removed. The detrusor contracts until the bladder is emptied. This sustained contraction occurs only if the connections between the micturition center and the subcortical centers are intact. The internal urethral orifice opens only when the detrusor contracts and when the intravesicular pressure rises to between 30-50 cm. During micturition the pressure rises to approximately 50 cm. of water, and remains there until the bladder is empty.

At any point during micturition the act can be terminated by voluntary contraction of the external sphincter. The external sphincter is assisted by contraction of the muscles of the pelvic floor.

CLASSIFICATION

It must be recalled that there is a difference in level between the vertebrae and the origin of the nerve roots leaving the cord. For example, lesions above T.12.L.1 spare S.2.3.4, leaving an intact micturition center and simple reflex arc (upper neurone lesion). Lesions below this level destroy the center and the reflex arc (lower neurone lesion).

1. Upper neurone lesion (reflex or automatic bladder)
   a) complete
   b) incomplete
2. Lower neurone lesion (non-reflex or autonomous bladder)
   a) complete
   b) incomplete
3. Lesions of posterior social roots (atonic bladder).

The upper neurone lesion gives rise to the reflex or automatic bladder. There is involuntary evacuation of urine at more or less regular intervals varying from one to several hours depending on the rate of fill. There is loss of vesical sensation and the "desire to void". Many have "aurae" of impending micturition such as sweating, headache, or abdominal discomfort. There may be certain "trigger points" supplied by the nerves from the sacral segments, so that pinching the perineum, anus, scrotum or vulva may induce micturition. The residual urine and the capacity of the automatic bladder is very variable.

The lower neurone lesion gives rise to the autonomous or non-reflex bladder. The site of the lesion is in the sacral segments of the cord, cauda equina or the pelvic nerves (nervi erigentes). There is loss of vesical sensation with loss of the "desire to void", although a vague sensation of suprapubic or perineal fulllness may be transmitted via the presacral nerves. All voluntary control of micturition is lost. Some urine may be expressed by manual increase in intra-abdominal pressure. This is a very inefficient type of bladder which may have a large residual urine, or more commonly is a small contracted bladder with obstruction to the uterers producing hydronephrosis.

The term "complete" in this classification refers to complete transection of the cord. The term "incomplete" includes lesions either not severe enough to produce transection of the cord or that there has been a degree of recovery following an apparently "complete" lesion. The resulting type of vesical function can vary from very severe impairment to an almost normal bladder.

Lesions of the posterior sensory sacral roots gives rise to the atonic or flaccid bladder. This type of bladder is seen in tabes dorsalis. Only the sensory fibres of the reflex arc are involved. There is loss of vesical sensation with loss of the "desire to void". The bladder has a very large capacity with a very low intravesical pressure. Such patients have overflow incontinence and a high residual urine.

ETIOLOGY OF THE NEUROGENIC BLADDER

1. **Traumatic — complete or incomplete transection of the spinal cord.**

2. **Congenital**
   a) Spina bifidaocculta, meningocele, or meningomyelocele
   b) Diastematomyelia

3. **Inflammatory**
   a) Poliomyelitis
   b) Transverse myelitis
   c) Tuberculoma of the cord

4. **Degenerative**
   a) Cardiovascular accidents
   b) Disseminated sclerosis
   c) Syringomyelia
   d) Subacute combined degeneration
   e) Tabes dorsalis
   f) Diabetic tabes
   g) Arteriosclerosis and senility

5. **Neoplasms**
   a) Primary (benign and malignant) of cord, coverings or bone.
   b) Secondary.

STAGES OF TRAUMATIC NEUROGENIC BLADDER

1. **Acute stage (phase of spinal shock).** Every case of spinal cord trauma experiences a phase of spinal shock with (a) loss of sensation below the injury level, (b) loss of motor power below the level which includes the detrusor muscle, and (c) loss of sphincter control. There is complete loss of reflex activity below the lesion. The bladder is hypotonic and there is loss of bladder sensation and the "desire to void". The bladder drains by overflow dribbling. This stage can last for days or months.

2. **Recovery stage.** This stage is characterized by the return of reflexes and sensation. This varies with the severity and completeness of the lesion. As skeletal reflexes appear, contractions will also appear on the cystometrogram. These are uninhibited contractions and are not voiding contractions. The patient will only void when a contraction occurs that raises the intravesical pressure to 50 cm. of water and maintains it at this level.

BASIC PROBLEMS

1. **Acute phase.** The most important obligation of the doctor to the patient in this phase is to prevent over-distention of the bladder. Over-distention results in trauma to the detrusor by over-stretching. Nature responds to this with inflammatory edema of the bladder wall and inflammatory exudate into the bladder lumen. The inflamed edematous bladder is more susceptible to infection than is the normal bladder.

2. **Recovery phase.** The doctor during this phase must again prevent over-distention and infection and must maintain an adequate bladder capacity (250-300 cc.). He is also faced with the problems of catheter care, of maintaining adequate hydration and caloric intake to ensure a high urinary output, and of preventing the catabolism of body protein and mobilization of calcium.

TREATMENT

1. **Aim.** The aim of the therapy is to provide the patient with a normal functioning bladder, failing this a bladder which will empty.

2. **General treatment** includes treatment of the initial shock and accurate diagnosis of the cord lesion followed by early surgical attack when indicated. All such patients should be cared for in a specialized center, nursed on a striker frame and turned every 2 hours.

3. **Prophylaxis** includes the prevention of the basic problems of over-distention and infection which will eventually lead to

fibrosis and a bladder of fixed capacity. This in turn causes lower ureteral stenosis and hydronephrosis.

4. Active.

During the acute phase intermittent catheterization or manual expression is dangerous. A number 16, 5 c.c. Foley catheter should be inserted and changed every 10 days under strict aseptic conditions. The urethra should be carefully irrigated with an antiseptic solution before a new catheter is inserted. The catheter should be connected to a closed drainage apparatus with periodic bladder lavage, irrigating 4 times per day with half-strength G-solution, filling the bladder to 250 cc. The catheter in the male is brought up over the abdomen so as to remove all pressure from the peno-scrotal junction, thereby preventing pressure necrosis and abscess formation. The drainage tube is fixed to the bed just below the axilla.

Suprapubic cystotomy is rarely necessary and is undesirable. It may be necessary in cases of severe uethritis and peri-urethral abscess.

Cystometrograms should be done weekly to determine emptying contractions and the return of reflex activity. They should be continued throughout the acute phase.

Urinary infection must be prevented. The urine should be kept slightly acid to control the urea-splitting organisms. The urinary output should be maintained at 3000 cc. per day. The perineum and genitals should be carefully washed at least daily. Prophylactic antibiotics and sulpha therapy is controversial. Some authors prescribe continuous therapy, others periodic courses, while others prefer to wait for the infection and vigorously treat it specifically. There is no antibiotic that will substitute for cleanliness.

At three months there should be both an intravenous pyelogram and a systoscopy carried out. Blood urea estimations will help estimate kidney function.

It is difficult to know when to discontinue catheter drainage and start bladder education. The patient should be in good condition and up in a wheel chair and beginning to learn to use crutches. This usually takes 3 to 6 months. The catheter is removed when there is evidence of an emptying contraction on the cystometrogram. 250-300 cc. of aseptic solution are inserted into the bladder and the catheter is then removed. If the patient fails to void adequately within one hour, the catheter is reinserted. Such training is continued until adequate voiding is established.

Now arises the problem of chronic care. Residual urines must be done to test the efficiency of the bladder. If the residuum is more than 30 per cent of the total bladder capacity, surgery must be considered.

In patients who are incontinent, a condom type of drainage might be preferable to catheter drainage for long term use.

Intravenous pyelograms should be done yearly and the patients should be checked by their doctor every three months.

Surgical Treatment of the Chronic Neurogenic Bladder

All forms of conservative therapy must be exhausted before the patient is exposed to surgical intervention. All advances in treatment have been directed towards reducing the tonicity or spasticity of the vesical sphincter, the bladder neck, the external sphincter and the muscles of the perineum.

1. *Transurethral resection of the vesical neck*

This operation was first used at the Mayo Clinic in 1937. It has been found most satsfactory in the non-reflex bladder, especially if the lesion is low enough to spare the abdominal muscles. Cases with a large residual urine and marked hypertrophy of the detrusor with an obstructed bladder neck respond well. There is a marked reduction in the residual urine and tendency to infection is less following resection.

2. *Methods to decrease the spasticity of the external sphincer and perineal muscles*

If bladder neck resection fails, consideration should be given to the fact that the external sphincter is spastic as a response of skeletal muscle to an upper motor neurone lesion. Pudendal nerve block and section has been used with some success. Munro suggested anterior rhezotomy of T.11 to L.5, sparing the sacral roots, to abolish extravesical mass reflex which excites bladder contraction. Bors suggested subarachnoid injection of alcohol to eliminate this mass reflex and found marked improvement in bladder function due to relaxation of the external sphincter. Alcohol injection, of course, can only be used in complete lesions. Many patients refuse this treatment because it abolishes penile erection, for even in complete lesions many patients are capable of coitus. It must be remembered that this procedure if carried out in an upper neurone lesion may destroy the micturition centre which will convert a reflex bladder to a non-reflex bladder and produce more extensive anesthesia. It also destroys this mass reflex of the lower limbs which, apart from being painful, renders any form of bladder control impossible.

3. *Division of he external urethral sphincter*

This is a new operation recommended by Ross *et al* in paraplegics who have not responded to the above more orthodox methods. This operation is "the division or resection of the external sphincter to relieve the retention of urine or high residue in patients with an open bladder-neck and a narrow rigid external sphincter area."

4. *Topical anesthesia of the vesical mucosa*

Recently Bors suggested the use of topical mucosal anesthesia as a simple non-surgical procedure for the treatment of patients with an upper motor neurone lesion, but may also be helpful in cases with a lower motor neurone lesion. It was found of value in some cases with preceding transurethral resection of the vesical neck which alone did not establish function. Bors injected 2-3 ounces of ¼% aqueous solution of pontocaine into the bladder for 10 minutes. This method established or restored bladder function in 28 per cent of patients he treated.

5. Certain selected cases of paraplegia are best handled from a urological standpoint by giving the patient an ileal conduit.

The author wishes to express appreciation to Dr. Lloyd N. McAninch for his interest and suggestions in preparation of this article.

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The Nephrotic Syndrome

JAMES R. BROW, '60

INTRODUCTION

The term "nephrosis" is a rather non-specific term which was first used by Muller in 1905, who designated it to be a disease state of the kidneys which consisted primarily of a degeneration of the renal tubules. Since that time new techniques have revealed lesions of the basement membrane of the glomerulus.

Because it does not commit one to any definite notion of the renal lesion and also because the clinical picture of the nephrotic syndrome may be present in a number of disease states, differing widely in etiology, the term "the nephrotic syndrome" is more commonly used today.

The nephrotic syndrome is a clinical state characterized by:

1) massive proteinuria
2) hypoalbuminemia
3) marked edema
4) hypercholesterolemia

In its most characteristic form it is seen in children and young adults as the so-called pure or lipoid nephrosis. Subacute glomerulonephritis is the pathological basis for a high proportion of cases. It is seen in other disease states but the fundamental basis for its development still remains one of the very complex and outstanding mysteries in medicine. In children, it is seen somewhat more commonly and occurs on the average at about 2½ years of age. It is more common in boys than girls.

ETIOLOGY

The exact etiology for the development of the nephrotic syndrome is still in question. It may be a manifestation in any of the following etiologically different clinical conditions:

1) the nephrotic stage of glomerulonephritis
2) amyloid disease of the kidneys
3) lipoid nephrosis
4) syphilitic nephrosis
5) disseminated lupus erythematosus
6) intercapillary glomerulosclerosis (Kimmelstein-Wilson syndrome)
7) thrombosis of the renal vein
8) toxic reaction to certain of the anti-epileptic drugs (for example tridione)
9) poisoning with certain chemicals (for example carbon tetrachloride)

Lange *et al* believe that nephrosis or the nephrotic syndrome is a distinct disease with an immunologic basis and is characterized by a complement-binding antigen-antibody reaction. This theory, he states, pertains only to the nephrotic stage of glomerulonephritis and to lipoid nephrosis.

Most internists believe the nephrotic syndrome to be a form of glomerulonephritis, whereas the pediatricians lean more towards an intrarenal disturbance of protein metabolism or from a specific renal lesion.

Findlay states, "It would be surprising, indeed, if the nephrotic syndrome does not prove to be of endocrine origin!"

SIGNS AND SYMPTOMS

The onset of the nephrotic syndrome should be correlated in part with the etiology of the persisting disease state.

The development of edema is of a very insidious nature. The edema, which at first is gravitational and later generalized, is the chief abnormal finding on physical examination. Anorexia and intestinal disturbances may accompany the ascites. Hydrothorax may occur with its sequelae. The skin of the abdomen, thighs, and legs is shiny and stretched. Cracks in the skin, when they occur, may ooze a serous fluid.

In patients with the nephrotic stage of glomerulonephritis or inter-capillary glomerulosclerosis, the presence of congestive heart failure may completely overshadow the onset.

Pallor is a manifestation.

In the early stages there is scanty urine of a high specific gravity. The marked proteinuria is accompanied by hyaline casts and occasional granular casts, rare red blood cells, and occasional pus cells.

There is a hypercholesterolemia and a decrease in the serum albumin. The sedimentation rate is usually high and has been attributed to the hypercholesterolemia and the high serum globulin. A reversal of the A:G ratio is usually present.

In the classical clinical state there is no hypertension, nitrogen retention, or appreciable decrease in kidney function.

PATHOLOGY

The specific lesion in the nephrotic syndrome depends upon the clinical condition present. The following material pertains to the microscopic picture as seen in the kidneys in the more prominent disease states.

The degree of glomerular pathological change in pure or lipoid nephrosis has probably drawn the most attention due to the so-called obscurity of such a lesion. The basic change in this condition is a hyperpermeability of the glomerular capillaries for albumin. According to Boyd, the glomerular capillary membrane is thickened, due probably to a deposit of protein between its inner and outer layers. Some splitting of the membrane occurs. No glomerulus is spared. The thickening and splitting of the glomerular membrane has led to the term "Membranous Glomerulonephritis of Ebstein." The tubular lesion consists of deposits of fat in the proximal convoluted tubules and fat can also be found in the tubular lumen.

In glomerulonephritis various stages of degeneration of both the tubules and glomerulus may be seen. Hyalinization of the glomerulus capillaries, the formation of adhesions between the tuft and the capsule, and the formation of epithelial crescents may all be seen. Various forms of degeneration (for example, albuminous, fatty, hyaline, etc.) may be seen in the kidney tubules, particularly the convoluted tubules.

In amyloid nephrosis amyloid is deposited between the two layers of the glomerular capillary membrane with subsequent damage to the filter and the usual nephrotic sequelae. It is also deposited just beneath the vessel wall in the peritubular capillaries.

In intercapillary glomerulosclerosis (Kimmelstiel-Wilson syndrome) the glomerular tuft lesions may be sparse or diffuse. The lesions occur opposite the vascular pole of the glomerulus and consist of a deposit of laminated and homogeneous hyaline material between the glomerular capillaries. The ultimate stage reached is that of complete hyalinization of the capsular mass. The afferent and efferent arterioles also show deposits of hyaline in their walls.

In disseminated lupus erythematosus the glomerular lesion consists of a patchy thickening of the capillary membrane to give the glomerulus the classical "wire-loop" effect. Fibrinoid necrosis of the small arterioles, frequently the afferent arterioles, is seen.

PATHOLOGICAL PHYSIOLOGY

A. Proteinuria

This can be explained on the basis of the definitive glomerular damage and escape into the glomerular filtrate and hence into the urine of protein from the plasma. There are subsequent changes in the plasma proteins where one observes a marked decrease in serum albumin and an increase in the total globulins. The alpha and beta fractions are increased, whereas there is a decrease in the gamma-globulins.

With respect to lipoid nephrosis and the nephrotic stage of glomerulonephritis, Lange *et al*, with their theory of a complement-binding antigen-antibody reaction, state that there is a probability that not only the glomerular capillaries are damaged but also many other capillaries in the body, producing a general increase in glomerular and capillary permeability.

B. Hypoalbuminemia

The pathogenesis of the hypoalbuminemia is not understood. Some investigators attribute it entirely to the proteinuria, whereas others believe this to be inadequate because the rate of protein synthesis is often greatly increased and the quantity of protein excreted is often relatively small. Even by high protein feeding or by the infusion of albumin, it is difficult to raise the levels of plasma proteins transiently or even to a slight degree. Farr states that on a diet of 3 gram protein per kilogram body weight up to 110 gram, it would be necessary to give 750 grams of protein to raise the serum protein 1 gram %.

C. Edema

The edema has been attributed to a decreased glomerular filtration rate, but in the nephrotic syndrome the filtration rate can be reduced, normal, or even supranormal.

The retention of sodium is also a factor in its formation.

It has been pointed out that many of the patients suffering from this condition also suffer from malnourishment which would eventually lead to a decrease in the tissue back pressure and hence promote edema.

The hypoalbuminemia would tend to decrease the colloid osmotic pressure of the plasma and hence promote edema formation. This is based on the work of Starling, who demonstrated the significance of the osmotic pressure of the plasma proteins in the passage of water in and out of the capillary. All of the above factors may play a role in its formation.

D. Hypercholesterolemia

The mechanism behind the production of hypercholesterolemia is not thoroughly understood. It may be related to a lipid mobilizing factor which has recently been isolated from animals. The hypercholesterolemia consists of both free and esterified cholesterol and phosphlipid fractions.

CLINICAL COURSE

In children the nephrotic syndrome is a fluctuating condition. It is characterized by episodes of exacerbation of proteinuria and edema. Some children remit spontaneously, losing edema and proteinuria permanently. Others continue to pass protein with impairment of renal function for long periods. A small proportion die of renal and cardiac failure or other causes. Absence of proteinuria for many months does not preclude a relapse. This makes it impossible to evaluate the results of treatment over short periods.

In adults, although the disease is not frequent, uremia, hypertension and cardiac failure are the terminal events usually.

Before the advent of antibotics pneumococcal pneumonia and peritonitis were frequent causes of death, remembering that patients with this condition have a characteristic low plasma gamma-globulin fraction.

TREATMENT

It must be mentioned first that a positive therapy for the nephrotic syndrome has not been found. The following is a summary of some of the therapeutic measures which have been used with indications where some success has been achieved.

A. Diet

1) rich in protein. 100 to 120 grams per day. The necessity of this is to maintain a good state of nutrition in an illness of long duration associated with a loss of much body protein. It is also necessary to maintain a positive nitrogen balance and to promote synthesis of plasma proteins. A general rule with respect to protein requirements has been propounded — give the normal amount of daily protein plus addition for that which has been lost in the urine per day.

2) Vitamin D and calcium should be supplied in the diet.

3) Sodium chloride in diet limited to not more than 2 grams per day.

4) oral supplements of potassium, in the form of citrate and acetate salts, should be given when attempting therapy. When diuresis occurs, large amounts of potassium are lost and hence the danger of hypokalemia.

B. Control of Edema

1) prevention of water retention
This might be minimized up to a point with the reduction of fluid intake and the restriction of salt.

2) attempts to raise the colloid osmotic pressure of the plasma

   (a) gum acacia in 6% solution was once used but was found to be toxic to the liver and possibly to the kidney.

   (b) whole blood and plasma transfusions have been given with rather poor results.

   (c) gelatin has been used but has been found to be too toxic.

   (d) the infusion of 12% Dextran in a glucose-and-water solution has been used experimentally but the metabolic handling of it has not been finalized.

   (e) salt-free human albumin has been given with subsequent diuresis in 50% of cases treated, although without lasting alterations in the level of serum albumin, and without effect on the course of the disease. There is risk here of homologous serum jaundice.

3) removal of the edema

Urea, besides being very unpleasant to take, has been found to be less effective in the removal of the edema than the mercurial diuretics. Even the mercurial diuretics combined with acid salts have had disappointing results in the majority of cases. Lately chlorothiazide (Diuril) has proven to be quite effective. Paracentesis should be done only if there is cardiac or respiratory embarrassment due to the generalized edema.

C. Hormone Therapy

This line of treatment seems to be the trend today with the ultimate aim at producing a diuresis.

ACTH and Cortisone have produced diuresis in about 60% of recent reported cases. ACTH has been the more effective of the two and the results as a whole better in children. No claim has been made yet that hormone therapy produces cure.

Dose — Cortisone: 150-250 gm. daily I.M. for ten days, when it should be withdrawn without tapering off. ACTH: 40-80 units daily.

Penicillin is given daily with the above to minimize the risk of intercurrent infection.

Good results have been reported with the use of Prednisolone in children — 60 mg. daily orally in divided doses for ten days, followed by 40 mg. for 10 days, and so on, the course lasting 40 days. Prednisolone has less salt-retaining action compared to ACTH and Cortisone. Although it is not known yet whether the children are cured, the results warrant further trial.

PROGNOSIS

Approximately 50% of children with the nephrotic syndrome are cured without any apparent sequelae. Signs of renal failure may have been manifested during the course of their disease. The other 50% tend to go on to chronic glomerulonephritis and its sequelae.

In amyloid disease and the Kimmelstiel-Wilson syndrome the prognosis of the nephrotic syndrome is that of the underlying disease process.

Syphilitic nephrosis is a curable type of nephrosis.

The appearance of hypertension and nitrogen retention in patients with the nephrotic syndrome is an ill-omened prognostic sign.

The majority of adults tend to go on to chronic nephritis but with the comparatively recent employment of the corticosteroids in therapy there is some evidence to show that they might aid in alleviating the poor prognosis here.

To J. C. Rathbun, F.R.C.P.(C), F.A.A.P., the author wishes to express appreciation for interest shown in the writing of this article.

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THE PRINCIPLES AND PRACTICE OF MEDICINE — Sir Stanley Davidson, Fourth Edition, E. and S. Livingstone Ltd., Edinburg and London. 1958. (In Canada by MacMillan of Canada Ltd.). 1067 pages, $6.00.

This book is a practical text of medicine for both student and practitioner. Within six years four editions of this text have been published with the result that the book is lucid, very readable, and up to date. No attempt is made to describe every rare disease or syndrome but an attempt is made to devote most of the space available to those disorders most commonly encountered in practice. The author has started each chapter of the book by going back to basic principles and fundamentals in order to encourage a rational approach to an understanding of symptomatology and treatment.

This book may be recommended not only for its excellence of style and clarity of presentation, but also for its modest price.

—M. Taylor, '59

Contemporary Concepts of Human Sex Anomalies

ROBERT C. LINTON, '59

INTRODUCTION

The study of human sexual anomalies has increased in significance in the past ten years. Workers in histology, embryology, endocrinology and clinical medicine and surgery have focused much attention on this subject with gratifying results. In this brief paper an attempt is made to present the current thinking with respect to certain syndromes that may confront the urologist or any medical practitioner.

HISTORICAL NOTE

To understand sex anomalies in their present context reference must be made to the work and theories of the past. The description of human ambisexuality dates back to early times. Plato described the original human nature as having three sexes — man, woman, and a combination of the two. Theophrastus first mentioned the bisexual deity Hermaphroditus whom Diodorus spoke of as being born of Hermes and Aphrodite. Artists and sculptors have since recorded this myth in drawings and stone and the term "hermaphrodite" found its way into medical literature to describe subjects with ambisexual genitalia.

In recent years many papers have added further details to an understanding of sex anomalies. Turner (1938) described a syndrome characterized clinically by sexual infantilism, webbing of the neck and cubitus valgus in girls and women. Klinefelter *et al.* (1942) described a syndrome in males with gynecomastia, azoospermia, increased urinary excretion of gonadotrophic hormone and hyalinization of the seminiferous tubules.

In experimental embryology, Jost (1950) showed that if gonads were removed in the early development of rabbit embryos, the reproductive tract developed in the female direction regardless of embryonal sex. From this and other experimental work, it became apparent that an inductor or evocator substance from the fetal testes was necessary for normal maturation of the male reproductive system.

In the histological investigation of this subject, Barr and Bertram (1949) introduced the new concept of "nuclear sexing" when they observed in neurones a special mass of chromatin found in nuclei of females but not in nuclei of males. Moore, Graham and Barr (1953) demonstrated in skin biopsies that cells of the stratum spinosum in females had a special sex chromatin mass subjacent to the nuclear membrane. The corresponding cells in males lacked the sex chromatin mass. Davidson and Smith (1954) observed that nuclei of neutrophils in women have a "drumstick" appendage attached to one of the nuclear lobes. Such nuclei occur with a mean frequency of 2 to 3% in blood films of chromosomal females and are entirely lacking in blood films of chromosomal males. Moore and Barr (1955) developed the oral mucosal smear method of "nuclear sexing". In a smear of good technical quality the characteristic

sex chromatin mass occurs in 40 to 60% of nuclei of chromosomal females and again is lacking in nuclei of chromosomal males.

The simplicity of the oral smear method of sex determination has greatly facilitated clinical and research studies . Barr (1956) subsequently pointed out that for psychological reasons, it is advisable in clinical usage to use the terms "chromatin-positive" for nuclei containing sex chromatin (XX sex chromosones) and "chromatin-negative" for nuclei not containing the sex chromatin (XY sex chromosomes).

CRITERIA OF CLINICAL SEX

(after Jones and Scott, 1958)

1. Chromosomal arrangement (XX or XY)
2. Gonadal structure
3. Morphology of internal genitalia
4. Morphology of external genitalia
5. Hormonal status
6. Sex role of rearing
7. Gender role of individual.

The normal individual has all five organic and two psychological criteria corresponding as to sex. A sex anomaly exists when there is a discrepancy in one or more of the morphological criteria.

CLINICAL ENTITIES

1. Gonadal Agenesis (Turner's syndrome)

Description. This syndrome in humans is nature's counterpart of Jost's experiments on rabbit embryos. Eighty per cent of these individuals have chromatin-negative nuclei, showing that the fundamental error is testicular dysgenesis with feminization of the embryo in the absence of a masculinizing inductor. Those with chromatin-positive nuclei are examples of ovarian agenesis and they would have feminized in any case.

The internal and external genital structures are normally female but of an immature nature in Turner's syndrome. They include a vagina, uterus and Fallopian tubes but no functional gonads. It follows, therefore, that in the absence of functonal gonads secondary sex characteristics fail to develop at puberty. Streaks of connective tissue containing mesonephric elements with no gonadal component are present in the normal ovarian position in the mesosalpinx.

In addition to agenesis of the gonads there are associated congenital anomalies. Short stature is the rule and the following anomalies occur in some patients: webbed neck, cubitus valgus, coarctation of the aorta and various skeletal deformities. Before puberty the presence of gonadal agenesis may be suspected in a female child of short stature, especially if one of the above anomalies is present. The diagnosis is made certain by finding chromatin-negative nuclei in an oral smear (Barr, 1956). After the age of puberty, the failure of development of secondary sex characteristics is added reason for suspecting gonadal agenesis. A further diagnostic aid is the increased excretion of urinary gonadotrophins from the age of 9 to 10 years onward. Adult females present with amenorrhea and sterility problems.

Management. Early diagnosis is important and if it is established estrogen therapy should be started around the age of puberty. The usual practice is to give Stilbestrol, 0.5 to 1 mg. daily Progesterone may be given for a few days at monthly intervals (Rathbun *et al.*, 1958). The vaginal bleeding that occurs on withdrawal of progesterone simulates menstruation and has a favorable psychological effect.

2. Hermaphroditism

(a) Male Pseudohermaphroditism

Description. A male pseudohermaphrodite is a person who has ambiguous geni-

talia associated with testes which may be in the pelvis or inguinal canal. These individuals have chromatin-negative nuclei without exception. There is a considerable variation in the degree of feminization of the internal and external genitalia. This anomaly appears to be a result of functional deficiency of the fetal testes in producing the masculinizing inductor. Thus the differences in degree of inductor failure and the stage of development when failure occurred produce the individual varations in feminization. This picture presents through all the variants of decreasingly feminine genitalia to a relatively masculine patient with hypospadias and a bifid scrotum.

The "syndrome of feminizing testes" is in a sense an extreme form of male pseudohermaphroditism. These patients have the added feature that the interstitial cells of the testes secrete estrogens after puberty. They are frequently tall, have well developed female secondary sex characteristics and appear strikingly feminine on routine clinical examination. These patients frequently seek advice because of primary amenorrhea or may consult a physician because of infertility.

Management. In doubtful cases at birth it is preferable to delay the assignment of sex until a thorough investigation has been done. Delay is preferable to a wrong decision which may have to be reversed later. In making a diagnosis the role of the oral smear is to distinguish this syndrome from female pseudohermaphroditism (*v.i.*). Estimation of urinary 17-ketosteroids is an equally good diagnostic procedure. As described below, the values are high in the adrenogenital syndrome which is responsible for most cases of female pseudohermaphroditism, while the values are not elevated in male pseudohermaphroditism. The anatomy of the external genitalia is a decisive factor in deciding whether the child is to be raised as a male or a female. As a general rule, it is preferable that the child be raised as a female unless there is a reasonable chance of reconstructing adequate male genitalia by plastic surgery. Suitable hormonal therapy from puberty onward produces the desired secondary sex characteristics. In the case of the patients with the "feminizing testes syndrome", the estrogen secretion from the testes provides adequate secondary sex characteristics. The advisability of the removal of testes in the male pseudohermaphrodite has to be considered in view of the higher incidence of tumor development in undescended testes as compared with descended testes. Appropriate hormonal therapy as previously mentioned will then be required.

(b) True Hermaphroditism

This anomaly is rare. The criterion for a true hermaphrodite is the presence of both testicular and ovarian tissue. Some patients have an ovary on one side and a testis on the other but it is more common to find an ovotestis on one or both sides (Barr, 1954). Some true hermaphrodites have chromatin-positive nuclei, in a ratio of 3:1. A laparotomy and histological examination of gonadal biopsies must be done to establish a diagnosis. The morphology of the external genitalia determines the ultimate management of these individuals regardless of whether they have chromatin-positive nuclei or chromatin-negative nuclei.

(c) Female Pseudohermaphroditism

Description. This syndrome is characterized by the presence of ovaries, female ducts and varying degrees of masculine differentiation of the urogenital sinus and external genitalia. The nuclei are always chromatin-positive.

The anomalous development is usually the result of hyperplasia of the androgenic zone of the fetal adrenal cortex which vidilizes the infant. This particular condition is called the adrenogenital syndrome. The diagnosis is based on a chromatin-positive oral smear in a patient

whose external genitalia are ambiguous, i.e. a persistent urogenital sinus with hypertrophy of the clitoris. The male counterpart of the adrenogenital syndrome is characterized by accelerated prepuberal development producing sexual precocity. Associated metabolic disturbances dependent on the adrenal cortex may be linked with the virilizing component. Hence there may be virilism with salt-loss, resulting in an Addisonian crisis, or rarely virilism with hypertension (Grumbach and Barr, 1958).

Congenital female pseudohermaphroditism may also be caused by androgens from a maternal source during pregnancy. Recent studies have revealed several cases of masculination of female infants simulating the adrenogenital syndrome (Wilkins and Jones, 1958). The factor common to each case was the administration of synthetic progestins to the mother because of threatened abortion. Rarely, this syndrome results from a virilizing ovarian tumor occurring in the pregnant mother.

In older children adrenal cortical tumors cause virilism in the female and precocious puberty in the male. Adrenal tumors are diagnosed by estimating the urinary 17-ketosteroids and studying their level again in 7 to 10 days after daily injection of 50 to 100 mg. of cortisone. The tumor is refractory to cortisone as shown by persistence of high 17-ketosteroid levels. This is the distinguishing feature from the adrenogenital syndrome in which the levels decrease on cortisone therapy.

Management. Patients with the adrenogenital syndrome should be treated indefinitely with cortisone given by mouth or by intramuscular injection. Where necessary a hypertrophied clitoris may be removed, preferably before the age of 2 years.

Virilism resulting from a maternal source of androgens does not require treatment. An adrenal tumor found in an older child should be surgically removed.

3. Dysgenesis of Seminiferous Tubules (Klinefelter's syndrome)

Description. This syndrome is characterized clinically by abnormally small testes after puberty. The diagnosis is difficult to make before puberty except by cytological studies. A high percentage of these patients have chromatin-positive nuclei but some have chromatin-negative nuclei. They may seek medical advice because of infertility. Those having chromatin-positive nuclei represent an almost complete contradiction between chromosomal and phenotypical sex.

The histological appearance of the testes shows fibrosis and hyalinization of the seminiferous tubules with little or no evidence of spermatogenesis, hence the term "dysgenesis of the seminiferous tubules". The etiology is thought to be an abnormality of the sex-determining genes in those patients with the XX sex chromosome complex, with the development of testis-like gonads rather than ovaries. In those with the XY sex chromosome complex the genetic error produces deficient testes. In both instances masculinization results from the presence of abundant Leydig cells which secrete a masculinizing inductor (Barr, 1957). Clinical signs which may lead to a diagnosis of Klinefelter's syndrome are variable. There may be one or more traits of eunochoidism, or gynecomastia in a small proportion of patients. Current work shows that Klinefelter's syndrome is not infrequently associated with mental retardation.

Management. No treatment can be expected to correct the pathology of the testes. However, administration of testosterone has a favorable effect, especially when signs of eunochoidism are present.

SUMMARY

Certain aspects of research on sex anomalies have been mentioned. The description and management of the more common syndromes have also been discussed.

Special attention has been drawn to the significance of the oral smear method of detecting chromosomal sex which is useful in the diagnosis of suspected gonadal agenesis in childhood, the testicular feminization syndrome during and after adolescence, adrenocortical hyperplasia in infancy and seminiferous tubule dysgenesis.

ACKNOWLEDGMENT

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WERNICKE'S SYNDROME — H. M. Heller, New Eng. J. of Med., 259:1009-10, 1958.

An interesting advance in early diagnosis of this neurological syndrome associated with a vitamin B_1 deficiency, has been provided by correlation of ECG changes which prevail during the acute and early therapeutic stages of the disease. A brief review of the previously reported cases is provided, and has led the author to dwell more extensively on the cardiac manifestations which seem to simulate the findings in other thiamine deficiency conditions.

A classical case worked up by the author is submitted to illustrate the effect of adequate thiamine therapy on the cardiac findings. Extensive clinical and laboratory investigations were carried out to complete the picture and to exemplify the ECG changes in the fact of other normal findings. In addition the author illustrates a latent period of 3 months in which the ECG registered persistent T wave and S-T segment changes subsequent to initial thiamine therapy on the day of admission.

In his discussion, Heller describes the various ECG changes associated with beriberi and those of pellagra and has indicated a possible relationship between these diseases in the manner in which they affect the electrocardiogram. However, due to the delay in improvement of the clinical and ECG findings in the case of the thiamine deficiency he has implicated reversible structural neurogenic changes in the heart and possible multiple organ involvement, keeping in mind other major factors which may provide such changes.

—David Wilson, '60

Neoplasia of the Prostate

GORDON MARTYN, '59

INTRODUCTION

After middle age the prostate is the greatest single factor affecting urination. There may or may not be changes in normal architecture of the prostate. Certain glands may proliferate in a typical manner characteristic of benign "hypertrophy", or in an atypical manner characteristic of carcinoma. These are the changes occurring commonly after middle age which will be discussed.

CLASSIFICATION

A. Benign

1. Generalized glandular hypertrophy
2. Median bar formation
3. Solitary subcervical lobe
4. Combinations of the above

B. Malignant

1. Carcinoma
2. Sarcoma

EMBRYOLOGY

A series of solid buds arise from the endodermal part of the primitive urethra and the adjacent upper pelvic portion of the urogenital sinus. These buds grow into the dense surrounding mesenchyme. Five groups of lobes are arranged around the urethra, the posterior lobe developing a separate capsule and appearing to represent a special functional part of the gland. Prostatic hypertrophy chiefly involves the lateral and middle lobes, while the posterior lobe is more frequently the site of malignancy.

The prostate, a specialized portion of the urethra, is ½ glandular (derived from endoderm), ¼ involuntary muscle and ¼ fibrous tissue (derived from mesenchyme). The glandular pattern, as seen in the diagram, is most important for an understanding of the two pathological conditions. The mucosal and submucosal glands contribute to benign hypertrophy, while the true prostatic glands are the site of carcinoma. It is these true prostatic glands that make up the largest part of the surgical capsule which is left after enucliation.

ETIOLOGY

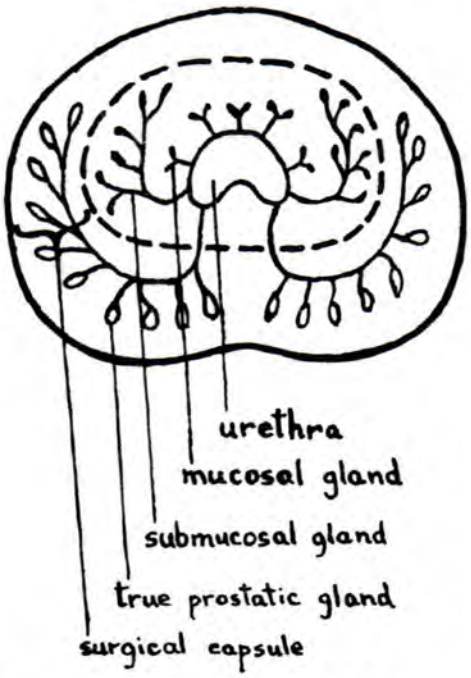
The prostate is an accessory sex organ. Its normal physiology depends upon the presence of androgen. Eunuchs have not been known to develop carcinoma or benign hypertrophy of the prostate. The actual cause of carcinoma or benign hypertrophy is unknown. The various etiological theories for benign hypertrophy include inflammation, arteriosclerosis, functional activity, endocrine and metabolic activity. However, it is generally thought that both benign hypertrophy and carcinoma of the prostate develop as a result of changes in the total and relative amounts of androgen and estrogen.

PATHOLOGY

1. Benign Hypertrophy

a) *Gross*

The gland usually enlarges in its lateral lobes. Normally it is the size of a walnut. When benign hypertrophy occurs, the gland may increase up to 40 times its normal size. The gland feels nodular, firm, and rubbery. Because the sites of enlargement vary, the actual amount of enlarge-



Diagrammatic Cross-section of the Prostate Gland

ment cannot always be clinically diagnosed rectally. A small middle lobe enlargement can cause symptoms of far greater severity than a lateral lobe enlargement of many times the former size. On cut section the nodularity protrudes above the surface.

b) *Microscopic*

The main feature is an exaggeration of the normal pattern. The lobularity is retained but there is an increase in the glandular, smooth muscle and connective tissue elements. There is both hypertrophy and hyperplasia. The acini are enlarged and cystic, the epithelium is papillary, and the cells are columnar. The stroma has lymphocytic infiltration.

2. Carcinoma

a) *Gross*

The posterior lobe is usually enlarged, and the malignant portion is very hard. On sectioning, it cuts with a gritty sensation and cross-section reveals the malignancy to be granular, grey in colour, and flecked with tiny yellow areas. No cysts are present, but there is usually a depression over the surface of the carcinoma.

b) *Microscopic*

About 97 per cent of prostatic carcinoma is adenocarcinoma. The glandular pattern is decreased and compressed by dense fibrosis. Pseudocysts are present and lined with low epithelium; mitotic figures are characteristically infrequent. The stroma contains atypical cells. The whole picture depends upon the degree of differentiation.

c) *Spread*

In 53 clinically diagnosed and histologically confirmed cases of prostatic cancer, the following was found: 17—no evidence of gross metastases, 37 — mestasized to bone, 22—metastasized to lymph nodes, 10—metastasized to liver, 7—metastasized to lung, 13—metastasized to miscellaneous sites. Distant spread is almost invariably present in patients dying of the disease.

An interesting finding has been made concerning the sex of the cells of these two conditions. The prostates of 78 cases of benign hypertrophy were sexed, and the findings showed equal distribution between male and female. Only 2 of 11 cases of carcinoma were contrasexed.

CLINICAL CHARACTERISTICS

Dysuria is the commonest single symptom of neoplasia of the prostate. However, urgency, frequency, burning, nocturia and other symptoms of bladder irritability may precede the more characteristic symptoms and signs of urinary obstruction. These characteristic symptoms and signs are dysuria, a narrow feeble stream, dribbling, hesitancy, stuttering flow, so-called "stop and go" urination, hematuria, and urination requiring straining. Acute retention

may be precipitated by exposure to cold, alcoholic excess, surgery and any vesical irritation. If obstruction has been neglected or has onset insidiously then uremia may be the presenting symptom—so-called silent prostatism. Signs of bladder enlargement may be present suprapubically. The end-result with respect to the urinary system can be vesical diverticuli, calculi, hydroureter, hydronephrosis and pyelonephritis with the corresponding symptoms and signs.

Pain in both benign hypertrophy and carcinoma of the prostate is rarely an early symptom. Because of this, the pathological process progresses until secondary effects are present. Carcinoma may progress unnoticed unless hypertrophy is present. Some authorities report that local pain is more likely to be associated with carcinoma. More typically the pain associated with carcinoma is not local; that is, low back pain, sciatica, and lumbago produced by disseminated tumor are characteristic.

The rectal examination may or may not reveal enlargement in the prostatic region. Benign hypertrophy, common in the lateral lobes and infrequent in the posterior lobes presents with firm, rubbery, nodular enlargement. Carcinoma, most commonly located in the posterior lobes, frequently presents with a stony hard area in the prostate which may be movable or fixed, with local extension in the adenexa.

The general condition of the patient may be modified by the pathological processes. Weakness, lethargy, and poor appetite are common to both benign hypertrophy and carcinoma of the prostate. Thirst may be increased with benign hypertrophy. Weight loss is more prevalent with the malignant process. Anemia which may be present in both cases can be acute in benign hypertrophy but chronically severe in carcinoma due to bone marrow invasion. A pathological fracture due to secondary invasion may draw attention to prostatic carcinoma for the first time.

LABORATORY

1. Urine

The urinalysis in benign prostatic hypertrophy may be normal. Hematuria is present in ¼ of the cases and is usually found at the beginning of urination. Gross hematuria does occur. If there is infection, pus cells, albumin and casts may be present, usually depending upon the amount of obstruction, infection, and other complications.

The urinalysis in carcinoma of the prostate is commonly normal. Hematuria is less frequent than with benign hypertrophy.

2. Blood

With benign hypertrophy there may be anemic and uremic changes.

In cases of suspected carcinoma of the prostate, attention is directed to the serum acid phosphatase. The true prostatic glands are the only glandular elements contributing to the acid phosphatase. The acid phosphatase activity is very high in the adult human prostate but it does not contribute to the circulation as long as the capsule of the prostate is intact. Many conflicting reports have been published concerning the serum acid phosphatase and carcinoma of the prostate.

The acid phosphatase taken directly from the prostate in a series of mainly operative cases and a few autopsies produced the following: 1) hypertrophy and prostatitis —increased levels, 2) carcinoma—decreased levels, 3) hypertrophy treated with stilbestrol — decreased levels, 4) carcnoma treated with stilbestrol—unchanged levels.

While it is generally believed that conspicuous elevation in serum acid phosphatase levels are pathognomonic of metastasizing carcinoma of the prostate, normal levels occur in about 35 per cent of patients with demonstrable disseminated prostatic carcinoma. These normal levels are usually seen in a very anaplastic carcinoma. Since hemolysis gives a high value to the serum

acid phosphatase, formalin fixation or alcohol inhibition should be used.

Prostatic acid phosphatase levels studied in 88 patients, 79 with carcinoma of the prostate, produced the following: 17 with local carcinoma—only 1 elevation, metastases or local spread—regular elevation, metastases after endocrine-induced remission — no elevation when disease again progressive.

DIAGNOSIS

History and Physical Examination

One must take a careful history that enquires not only into the presence of the symptoms and signs previously discussed, but particularly into the spacial relation of the symptoms and signs. A case that presents with dysuria with a history lasting 6 months is more likely to be carcinoma than benign hypertrophy of the prostate. In men who are retired the frequent urination may be part of their regular activity during an uneventful day. Also because of a tendency of wakefulness at night, the frequent trips may be quite ordinary. Such a life that is in fact governed by urinary frequency may be quite acceptable to an elderly man. If there is a decrease from the normal carefulness of middle age then there may be little concern or even little notice of a weak urinary stream that barely misses the shoes. One must be very careful in the interpretation of a history.

During the physical examination there are two observations that are most important. A rectal examination is the best single procedure used in diagnosis of prostatic neoplasia. The characteristics of the enlargements have been stated previously. Observation of the act of urination with an attempt to estimate the power of trajectory, should be more important than the modesty of patient or doctor. In addition to these two procedures a complete physical examination may reveal contributory information.

Laboratory

Urinalysis must be done.

Hematology with regard for anemia and uremia must be done.

Prostatic serum acid phosphatase must be done repeatedly. After a rectal examination this value may be elevated, thus the need for repeated tests.

Special Diagnostic Procedures

An intravenous pyelogram is the most informative special procedure. The amount of secondary kidney pathology, the knowledge that there are two kidneys, and their relative function can all be determined. By serial X-rays the condition of the bladder and, after voiding, the residual urine can be ascertained.

Cystoscopy and panendoscopy are the only means of actually visualizing the prostatic urethra. If a satisfactory diagnosis can be made on intravenous pyelography the second procedure can be deferred until the time of surgery.

Prostatic secretions examined by Papanicolaou staining in 250 cases led to the diagnosis in 9 carcinomas of the prostate while 15 were diagnosed histologically. No false positives were reported. From this report cytological methods appear unsuitable, at the present, for early diagnosis of prostatic carcinoma.

Biopsy either by transurethral resection, perineal needle biopsy, or excision biopsy through the perineum is the only way of making an accurate histological diagnosis.

DIFFERENTIAL DIAGNOSIS

Because dysuria is the commonest single symptom of neoplasia of the prostate, a differential diagnosis of this clinical entity must be considered.

1. Urethral Sources
   a) Stricture
   b) Calculi and tumors

2. Prostatic Sources
   a) Calculi
   b) Hypertrophy
   c) Carcinoma and Sarcoma
   d) Acute and Chronic Prostatitis
3. Changes at or close to the vesical neck
   a) Contracture of vesical outlet
   b) Median bar formation
4. Vesical Conditions
   a) Tumor
   b) Calculi
   c) Large diverticuli
   d) Hypertrophy of trigone or interureteric ligament
   e) Neurogenic conditions
   f) Senile atony

TREATMENT

1. Benign Hypertrophy

The objectives of treatment are a) to save a life, b) get rid of nuisance trouble. It is generally agreed that the only effective cure for this condition is surgical removal of the neoplastic mass. The indications for prostatectomy are:

a) To save a life:
   1. Acute retention
   2. Hemorrhage
   3. Uremia (may be suprapubic cystostomy)

b) Nuisance trouble:
   1. Urgency
   2. Dribbling
   3. Nocturia
   4. Frequency
   5. Hesitancy or stuttering

The routes of operation are: 1) transurethral, 2) perineal, 3) suprapubic, and 4) retropubic. The procedure is usually that of enucliation. The route chosen should be related to the patient's local and general condition, and the operator's ability with the procedure.

Before surgery adequate work-up of the patient's condition must be carried out with particular regard to infection, blood non-protein nitrogen, cardio-respiratory function, and kidney function.

Palliative, non-operative treatment, is permissible if 1) the residual urine is minimal, 2) the kidneys show no disease and their function is good, and 3) there are no diverticuli or calculi. When such therapy is undertaken, close regard for avoiding cold, trauma, alcoholic excess, and particularly infection must be taken. Urination must be frequent and the urge to urinate must be obeyed at the first impulse. Hormonal therapy for benign hypertrophy is not indicated.

2. Prostatic Carcinoma

The only *curative treatment* is radical prostatectomy, and then only in operable candidates. The candidate for radical prostatectomy must fulfill the following criteria:

a) disease limited to the prostate gland on rectal examination,
b) acid serum phosphatase normal on repeated studies,
c) skeletal survey negative for bone metastases,
d) patients under 70 who will stand a formidable operation.

It is reported that 1% of all patients with carcinoma of the prostate are amenable to radical surgery, however these figures vary considerably. Complications of radical prostatectomy are incontinence, impotence, and vesico-rectal fistula.

Palliative treatment takes two forms:

1. Relief of obstruction by transurethral resection or permanent suprapubic cystostomy.

2. Attempt to control the carcinomatous growth in both the primary and secondary lesions. Control of the cancerous growth is by hormonal therapy and local irradiation of painful metastases. Hormonal ef-

fect is obtained by a) reduction of androgen by castration, or in some cases by cortisone, bilateral surgical adrenalectomy, or hypophysectomy, b) administration of estrogen, varying the dose and route and compound until maximum effect is obtained. The results of palliative treatment are highly individualized.

PROGNOSIS

1. Benign Hypertrophy

Unless surgery is carried out the hypertrophy increases. Generally following surgery the result is good. The operative mortality is about 1 to 2 per cent and usually the result of severe urinary tract sepsis or pulmonary embolism.

2. Carcinoma of the Prostate

The ultimate prognosis is poor. However, early discovery and surgical removal of a small lesion confined to the prostate is curable. If the carcinoma is diagnosed late, then considerable palliation is possible. Untreated carcinoma without metastastes will live about 1 year, and with metastases about 9 months. The variation in activity of this malignancy is so great that a 5-year survival rate is almost impossible to derive. After radical prostatectomy, about 50 per cent live 5 years.

SUMMARY

Dysuria is common in varying degrees in men over 60 years of age. The commonest causes are benign hypertrophy and carcinoma of the prostate. Enucliation of the hypertrophy produces very good results. However, since occult carcinoma of the prostate is common it would appear that the procedure of prostatectomy would be favorable for benign hypertrophy. One must balance the complications of this procedure against the incidence of occult carcinoma. The conclusion probably is that enucliation is the treatment of choice for benign hypertrophy, and that better methods of diagnosis are needed for early recognition of prostatic carcinoma.

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Acute Renal Failure

G. NOEL CHANT, '59

INTRODUCTION

The syndrome of acute renal failure has been known by many other names, many of which relate to the etiological mechanism. Some such names are hemoglobinuric nephrosis, transfusion kidney, shock kidney, crush syndrome, acute anuria, lower nephron nephrosis, acute tubular nephrosis, and acute tubular necrosis. Although some writers include many other lesions of the kidney under the title term, in this article "acute renal failure" describes the syndrome due to acute tubular necrosis, featured by almost total failure of renal function for approximately two weeks, the pathognomonic manifestation being marked oliguria (below 400 ml. per day). The other mechanisms responsible for acute anuria or oliguria will be considered in the differential diagnosis.

ETIOLOGY

Many specific causes are listed, but principally the acute tubular necrosis results from nephrotoxic substances, transfusion reactions, crush injury, acute blood loss, sustained hypotension, or severe electrolyte depletion.

PATHOGENESIS

There are two main pathological subdivisions of acute tubular necrosis as determined by the microdissection technique of Oliver *et al.*

1. **Ischemic necrosis**—secondary to severe hypotensive or hemolytic episode. The ischemia of shock is a major cause. There is a severe uneven cellular degeneration in all parts of the tubule and irregular disruption of the basement membrane. The lumen is irregularly obstructed by cellular debris, by patchy cellular swelling and in some instances by hemoglobin derivatives, as well as by disruption in continuity.

2. **Nephrotoxic necrosis** — due to the effects of a specific toxin. There is a cellular degeneration in the proximal tubule but the basement membrane remains intact and the more distal portions of the tubule are spared. The poison is concentrated from the glomerular filtrate into cells of the proximal tubule which slough and spare the basement membrane. The cellular debris (forming casts) and the swollen degenerating cells obstruct the tubular lumen. Nephrotoxins often interfere with renal circulation as well.

Oliguria and rarely anuria are the result of both decreased glomerular filtration and increased reabsorption. The latter occurs particularly in the nephrotoxic type with denuded basement membrane permitting easy back-diffusion of the filtrate. The diuresis occurring in early recovery is the result of a restoration of luminal patency in some of the nephrons and passage of an almost unmodified glomerular filtrate.

DIFFERENTIAL DIAGNOSIS

1. **Functional oliguria and azotemia,** the result of diminished renal blood flow, is differentiated from mild acute renal failure by the former having a more concentrated urine.

2. **Other types of primary renal disease**
   a) Acute glomerulonephritis has its characteristic clinical features, a higher urinary specific gravity (1.018 or more), a strongly acid urine (pH under 5.5), and urine sodium under 30 mEq/L. Only rarely in this condition does marked oliguria or anuria occur.

b) Acute pyelonephritis is usually not confused but may be during diuretic phase of acute renal failure.

c) Acute exacerbation of chronic renal insufficiency is easily differentiated by evidence of a chronic disease, with wasting.

3. **Ureteral obstruction**

a) Urolithiasis, if suspected, requires gentle investigation of at least one kidney.

b) Sulfonamide crystalluria is diagnosed by cystoscopy and ureteroscopy. History alone is not enough since true acute tubular necrosis does occur when sulfonamide acts as a nephrotoxin.

c) Metastatic carcinoma is diagnosed by history and cystoscopy.

4. **Renal vascular lesions**

a) Nephrosclerosis may cause vomiting and dehydration.

b) Bilateral occlusion of renal arteries by emboli or thrombosis or aneurysm.

c) Bilateral cortical necrosis may follow abruptio placenta.

d) Bilateral thrombosis of renal veins.

Differentiation in the case of the latter lesions is difficult.

That any one of the above entities may occur in the single kidney of congenital anomaly or following nephrectomy must not be overlooked, especially in the case of urolithiasis or metastatic carcinoma.

Certain authors prefer to include the above listed other types of primary renal disease and renal vascular lesions as forms of acute renal failure.

CLINICAL COURSE

The clinical course, which may be reversable or terminal, short or long, is characterized by four phases.

1. **Phase of onset.** At this point the etiological condition predominates and occupies the attention of the clinician.

2. **Phase of oliguria.** Complete anuria is a rare occurrence. Urine formed has a fixed specific gravity of 1.010 and contains protein, casts, and red and white blood cells. Neurological changes develop after some days and consist of weakness, vomiting, and progressive stupor accompanied by twitching and convulsions.

3. **Phase of diuresis.** The beginning of recovery is signalled usually in the 2nd (or 3rd) week by an expanding diuresis, which is followed by a rapid clearing of the elevated non-protein nitrogen and a delayed recovery of concentrating power.

4. **Phase of convalescence** to complete recovery follows.

TREATMENT

As recently as the mid-1940's mortality rates in acute renal failure ranged from 80 to 90 per cent. Too often the cause of death was pulmonary edema as a consequence of over-hydration. Recent developments in physiological and artificial methods have reduced the mortality figure by one-half. Frequently damage to other systems, occurring at the same time as the renal lesions, is responsible for death during the course of treatment. The principle aim of treatment, in addition to treatment of the etiological mechanism, is the prevention of death, if possible, during the period of absent renal function. The latter is accomplished by attention to the avoidance of the two common causes of death—pulmonary edema from fluid excess and cardiac arrhythmias from potassium intoxication.

Under ordinary physiological conditions the kidney regulates the milieu intérieur with respect to waste excretion and fluid and electrolyte balance in spite of diversified influences and no matter what the nature or amount of intake and metabolism. Therefore, with cessation of this

regulation by output during acute renal failure, regulation must be effected by control of the nature and amount of intake and metabolism. The excretion of nitrogenous waste is never a serious problem since the accumulating non-protein nitrogen has less influence than the electrolyte abnormalities.

I Phase of Onset

Prompt emergency treatment of injury, poisoning, shock, and blood loss helps to minimize development of the acute tubular necrosis, and may prevent it. Administration of alkali is recommended to counteract the renal effects of hemolysis and sulfonamide poisoning. If there is sufficient doubt about the presence of dehydration, the patient should receive 1000 ml. of fluid in a form which simulates the deficit; that is, saline or saline-sodium lactate for gastro-intestinal loss and glucose in water for deficient water intake.

II Phase of Oliguria

1. Fluid Balance

An indwelling catheter for urine collection and daily weighings of the patient are essential to management. The patient should never gain weight, but in proper water balance should lose one-half to one pound of weight daily. The difference between the "gross" insensible water loss (cutaneous and respiratory) under ordinary circumstances (1000 ml. daily) and the insensible gain as a result of metabolism (near 500 ml. daily) is the "net" insensible water loss. The usual net water deficit is therefore 500 ml. daily for an adult, or 7 to 8 ml. per kg. body weight for children. The fluid replacement amounts to the net water deficit plus the measured output (gastro-intestinal and urinary) in the previous 24 hours. Special corrections are made for unusual circumstances. The 500 ml. of net water deficit is given as a 50 per cent solution of glucose in water by intravenous catheter opening into the inferior vena cava or by nasogastric tube or by mouth if the patient is not vomiting. The volume is given continuously if by vena cava or in frequent small feedings if by mouth, in which case vegetable oils may be added. The measured loss is replaced by fluid closest in composition to fluid loss; that is, urine by isotonic saline, emesis by isotonic saline, sweat by half-strength saline, etc., all given intravenously. Preferably the orders are detailed for each ursing working period 16 to 24 hours in advance.

2. Electrolytes

As early as feasible serum electrolyte determinations are made and an electrocardiogram recorded. These guides are used throughout oliguria to follow the serum potassium level and its effect on the heart, respectively. Since the effect on the heart is of course the more important, the ECG should be recorded more frequently, using the serum determinations as a general guide. The minimizing of potassium accumulation involves regulation of intake and catabolism. Fruit juices, meat, broth, etc. are strictly prohibited. Endogenous protein catabolism is reduced to a minimum (almost one-half) by the daily administration of 250 g. of glucose and/or fat, as described under fluid therapy. This supplies at least 1000 cal. daily. Thus, besides the sparing of protein, ketosis is eliminated. The influence of hyperkalemia on the heart is enhanced by hyponatremia which may occur, especially in the early stages. Water restriction is preferable to intravenous hypertonic saline in the correction of the latter. Rarely hypocalcemia with signs of tetany occurs, and may be easily controlled with intravenous calcium gluconate.

Artificial Methods for the Control of Hyperkalemia

Infusion of hypertonic glucose and insulin or of hypertonic saline to effect reduction of extra-cellular potassium pro-

duces transitory results (that is, for several hours).

Exchange transfusion is advocated in some European centres in the belief that there are toxic, non-diffusable materials in the blood of these patients. Since there is no present basis in fact its general use cannot be recommended.

Cation exchange resins have been reported to be effective in the gradual reduction of hyperkalemia. They are usually administered, in their ammonium or sodium phase, by retention enema.

Intestinal lavage is a method employing the irrigation of a segment of bowel between two intestinal tubes. At present, since it is a poorly-controlled method, its use should be limited to those cases wherein other methods have failed or are contraindicated.

Peritoneal lavage has wide variations in technique. The method was used extensively in the mid-1940's and has many proponents in Europe. It is effective and useful, but appears preferable to hemodialysis only in those in which bleeding presents a contraindication to heparinization.

Hemodialysis

Many techniques dating back to 1913 have been devised for the extracorporeal dialysis of human blood. All have in common certain technical difficulties and hazards. These include leaks or tears in the dialyzing membrane, errors in composition or temperature of the dialyzing fluid, hypertension or hypotension occurring during dialysis, and fatal hemorrhage as a result of heparinization. The use of the artificial kidney, usually about six hours in operation, involves heparinization of the blood and arterial and venous cannulation, and may have to be repeated. There are few more technically complex procedures in medicine than hemodialysis, and when combined with the complexity of precise physiologic management it presents a demanding responsibility with many opportunities for error.

The decision concerning the ideal time to institute dialysis is a difficult one and must depend on the experience of the physicians involved. Sometimes an arbitrary level of T-segment elevation is used as the criterion. There seems to be little support for the use of an absolute level of potassium concentration as a guide, and the non-protein nitrogen concentration is believed to have no significance in this regard. The above mentioned evaluation of criteria is with regard to the prevention only of mortality.

In regard to cost and safety it seems that the need for hemodialysis is sufficiently infrequent that patients in acute renal failure should be managed by an active and relatively permanent team in "renal centres" serving large populations.

3. General

The use of blood transfusion in the treatment of concurrent anemia is hazardous because of the delicate circulatory balance and the increased potassium concentration of bottled blood, and is justifiable (using washed cells) only for a hemoglobin less than 50 per cent. The prophylactic use of penicillin is recommended in all cases possible. Specific antibiotics are indicated for any infection present, avoiding if possible such nephrotoxic agents as streptomycin.

III Phase of Diuresis

Early in the phase of diuresis one must continue quantitative replacement of fluid and electrolyte losses, orally if feasible. Early restriction of fluid may cause dehydration since the diuresis is obligatory, probably largely due to impaired tubular reabsorption of water and salt. Observation of the clinical and electrocardiographic course ought to be continued, since electrolyte depletion may occur. Once urine volume exceeds 4 L. daily, careful moderate restriction of salt and

water may be begun. In failure to respond, fluid input is increased again. As soon as potassium levels have returned to normal, fruit juices or potassium supplements are allowed. Since the non-protein nitrogen falls more slowly, protein is restricted while that level exceeds 100 mg. %.

IV Phase of Convalescence

This phase of recovery to normal function involves gradually increasing activity, gradual decline in azotemia and gradual return of the capacity to concentrate urine. The azotemia usually clears at 2 to 3 weeks, but the loss of salt and water which usually begins to subside at 3 to 10 days may continue to a degree for months before full conservation ability returns. A full diet is permitted as appetite returns.

SUMMARY

Death should not occur from reversible acute renal failure, however prolonged. Physiologic methods of therapy will carry the vast majority through the episode and dialysis will allow the remainder sufficient time for repair of the renal lesion. In the words of Swann and Merrill, "In few other diseases does therapy so directly influence the clinical course and outcome as it does in renal failure. It cannot be said that this is a disease from which the patient usually recovers in spite of the physician. Rather it is a disease of which patients frequently die because of mismanagement."

Appreciation is expressed to Dr. N. M. Lefcoe for his interest and suggestions in preparation of this paper.

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THE DOCTOR'S PERSONALITY AS A FACTOR IN MEDICAL CARE — Henry A. Davidson, M.D. J. of Med. Soc. of New Jersey.

In this modern age of mechanization and group practice, it is too often forgotten that the personality of the doctor is a factor in the kind of medical care he gives.

The diagnosis of the etiology of disabilities, whether due to hysteria, organic disease or malingering, often rests as much on the doctor's prejudices as on the objective evidence. The physician's ability to handle deep confidences and yet preserve the dignity of the patient is a real test of the physician's skill. The author here demonstrates how the normal variations in the doctor's personality may effect the treatment of a neurotic. Because of this fact, different doctors may look upon the neurotic as either a sick man, a person suffering from a self-inflicted disease, or a parasite.

Some of the abnormal parsonality traits less frequently encountered but of a much greater concern to both the patient and physician are the doctors suffering from an obsessional neurosis or hypochrondiasis.

Therefore, the fortunate doctor is the one who, early in his professional life, has discovered his assets and liabilities and has tried to develop the kind of practice that best suits his temperament.

—Glenn Oliver, '60

Abstracts and Book Reviews

SPONTANEOUS STROKES IN THE YOUNG — H. Stevens, Ann. Int. Med., 49:1022-1034, 1958.

The spontaneous occurrence of strokes in healthy normotensive young subjects is not rare. Thirty-two such cases were encountered by the author in the last seven years, ranging in age from five and one-half to 44 years. No cases are included that had traumatic, infectious, neoplastic, hypertensive, vascular or any other primary disease.

Two large etiological groups could be recognized, those due to venous and those due to arterial thrombosis.

1. cerebral venous thrombosis
   (a) infantile hemiplegia
   (b) puerperal hemiplegia
   (c) venous thrombosis of pregnancy
2. cerebral arterial thrombosis
   (a) carotid artery
   (b) middle cerebral artery
   (c) other arteries of the circle of Willis, single or in combination.

Diagnosis of carotid artery thrombosis can often be made by clinical observation, including a history of acute onset of headache with contralateral hemiplegia, and ipsilateral Horner's syndrome. Palpation of the carotid artery and ophthalmodynamometry are valuable but not infallible technics that deserve more frequent usage. Arteriography is often indispensable, particularly to exclude intracranial aneurysm or tumor, but unnecessary, painful or dangerous tests can often he circumvented by careful analysis of clinical data, since the rationale of modern therapy does not compel the clinician to pinpoint precisely the locale of the cerebral thrombosis.

The cause of cerebral arterial thrombosis in the healthy young are solitary atheromatous plaques, analogous to if not identical with the atheromatous process that occurs in coronary vessels and elsewhere.

Stress has been blamed for increasing the susceptibility to or precipitating coronary thrombosis, and similar mechanisms have been invoked for cerebral thrombosis.

Unfamiliarity with spontaneous strokes in the young may motivate the perplexed clinician to subject the patient to a consecutive series of elaborate tests to uncover the elusive etiology. Syphilis and hypertension are easily and readily eliminated. Brain tumor, collagen disease, and congenital and acquired diseases of the vascular and hematologic systems are then sought after. The many tests necessary to investigate these various possibilities are usually negative. But the time consumed is often sufficient to permit spontaneous improvement. An erroneous diagnosis of multiple sclerosis is then often made by exclusion.

Development of a rational therapeutic program rests on accumulation and assessment of further data, especially on pathogenesis. The usefulness of anticoagulants in the treatment or prevention of a "stroke" requires further validation. Prognosis in these selected cases was generally good with no specific treatment. The indiscriminate use of anticoagulants without proper refinement of the heterogenous diagnosis of "stroke" is hazardous. Increased bleeding into a hemorrhagic infarct is a particular danger. Surgery on the carotid artery is still in an investigative stage, but may evolve into a safer and more satisfactory procedure in the future.

Further study of strokes in the healthy young would be particularly rewarding since the causative lesion can be studied in "pure culture", without contamination of the issue by the diffuse and multiple degenerative changes accompanying strokes in elderly patients.

—Ronald B. Passi, '60

Alumni and Faculty News

The following is a list of the positions held by graduates of 1956 as of December 31, 1958:

Dr. Harold Andry ..... General practice, Hamilton, Ont.
Dr. Faye Arundell ..... Dermatology, Cleveland Clinic, Cleveland, Ohio
Dr. Donald Bondy ..... Pathology, Westminster Hospital, London, Ont.
Dr. Harold Bartko .....
Surgery, Highland Park General Hospital, Highland Park, Mich.
Dr. Brian Brett ..... Medicine, Westminster Hospital, London, Ont.
Dr. Earle Brown ..... Endocrinology, Toronto Western Hospital, Toronto, Ont.
Dr. Stuart Burns ..... General practice, 419 Dundas St., London, Ont.
Dr. Ronald Butt ..... unknown
Dr. Grace Carruthers ..... unknown
Dr. Harvey Christiansen ..... Surgery, University Hospital, Saskatoon, Sask.
Dr. Gerald Cook ..... General practice, Saskatchewan
Dr. Keith Coulter ..... Pathology, Victoria Hospital, London, Ont.
Dr. Donald Ecker ..... General Practice, Exeter, Ont.
Dr. Christopher Ellis ..... Orthopedics, St. Luke's Hospital, Chicago, Ill.
Dr. Raymond Flowers ..... General practice, Thamesford
Dr. Douglas Hamilton ..... Surgery, Mount Carmel Mercy Hospital, Detroit, Mich.
Dr. Frederick Hartley ..... Surgery, Shaughnessy Hospital, Vancouver, B.C.
Dr. Kent Hay ..... Surgery, Grace Hospital, Detroit, Mich.
Dr. Kenneth Helson .....
Canadian Armed Forces, Europe (R.C.A.F. 3rd Fighter Wing)
Dr. Lewis Hersey ..... Anesthesiology, Victoria Hospital, London, Ont.
Dr. Marvin Himmel ..... Medicine, Montefiore Hospital, New York City, N.Y.
Dr. Rolland Kaplan ..... General practice, 418 Horner St., Toronto, Ont.
Dr. Melvin Kaspardlov ..... General practice, Amherstburg, Ont.
Dr. Marvin Kwitko ..... Ophthalmology, Episcopal Hospital, Washington, D.C.
Dr. Mervyn Lakin ..... Medicine, Wayne County Hospital, Eloise, Mich.
Dr. Joseph Langer ..... Plastic Surgery, Kings County Hospital, New York
Dr. Edgar Love .....
(Obstetrics and Gynecology), Anatomy and Physiology, U.W.O. Faculty of Medicine.
Dr. Douglas Manners .....
Obstetrics and Gynecology, Hamilton General Hospital, Hamilton, Ont.
Dr. Robert Martin ..... Obstetrics and Gynecology, Victoria Hospital, London, Ont.
Dr. John Mathers .....
Obstetrics and Gynecology, University of Minnesota Hospital, Minneapolis, Minn.
Dr. Donald F. McGregor ..... General practice, Oshawa, Ont.
Dr. Douglas D. McGregor ..... Pathology, Banting Institute, Toronto, Ont.
Dr. Frederick McKenzie ..... Medicine, Westminister Hospital, London, Ont.
Dr. Keith McNeil ..... General practice, London, Ont.
Dr. Robert McPhedran ..... Medicine, Toronto General Hospital, Toronto, Ont.
Dr. Duncan McPherson .....
(Surgery), Physiology, University of British Colombia, Vancouver, B.C.
Dr. Keith Mills ..... Psychiatry, Provincial Mental Hospital, Evondale, B.C.

Dr. Ellen Martin Moyer ..... Raising family in Toronto, Ont.
Dr. Jocelyn Pearce ..... Radiology, Toronto Western Hospital, Toronto, Ont.
Dr. James Peters ..... (Surgery), Anatomy and Physiology, U.W.O. Faculty of Medicine
Dr. Ingrida Raits ..... Opthalmology, Milwaukee County Hospital, Milwaukee, Wis.
Dr. Stephen Richardson ..... General practice, Prucher Creek, Alberta
Dr. Robert Shelley ..... R.C.A.F. Station, Rockcliffe, Ottawa, Ont.
Dr. George Sloan ..... Obstetrics and Gynecology, Grace Hospital, Detroit Mich.
Dr. Edward Sowa ..... Psychiatry, Toronto Psychiatric Institute, Toronto, Ont.
Dr. Thomas Staples ..... General practice, Hanover, Ont.
Dr. William Swan ..... General practice, Port Colborne, Ont.
Dr. Alfred Thibodeau ..... General practice, Lively, Ont.
Dr. Brian Thicke ..... R.C.A.F. Station, Rockcliffe, Ottawa, Ont.
Dr. Charles Thompson ..... General practice, Hamilton, Ont.
Dr. Robert Tuttle ..... R.C.A.F. Station, Gimli, Man.
Dr. Robin Waite ..... Pathological Chemistry, Victoria Hospital, London, Ont.
Dr. John Warkentin ..... Pathology, University Medical Centre, Kansas City
Dr. Barbara Garwood Waud ..... Anesthesia, Massachusetts General Hospital, Boston, Mass.
Dr. Douglas Waud ..... Pharmacology, Harvard Medical School, Boston, Mass.
Dr. George Willms ..... General practice, Windsor, Ont.
Dr. James Wright ..... General practice, Port Carling, Ont.

—R.D.W